

# ***AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report***

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## **Priority Area 11: Peptic Ulcer Disease and Dyspepsia**

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## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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## Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: [effectivehealthcare@ahrq.hhs.gov](mailto:effectivehealthcare@ahrq.hhs.gov).

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# Contents

Executive Summary .....	ES-1
Background.....	ES-1
Methods .....	ES-1
Results.....	ES-2
Discussion.....	ES-2
Peptic Ulcer Disease and Dyspepsia Interventions .....	1
Helminthic Therapy (Pig Whipworm) for Treatment-Resistant Ulcerative Colitis .....	2
PerOral Endoscopic Myotomy for Treatment of Esophageal Achalasia.....	5
Teduglutide (Gattex) for Treatment of Short Bowel Syndrome.....	9
References .....	12

## Figures

Figure 1. Overall high-impact potential: helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis.....	3
Figure 2. Overall high-impact potential: PerOral Endoscopic Myotomy for treatment of esophageal achalasia .....	7
Figure 3. Overall high-impact potential: teduglutide (Gattex) for treatment of short bowel syndrome.....	10

# Executive Summary

## Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs.

No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the five topics for which (1) preliminary phase III data for drugs and biologics or phase II data for devices and procedures were available; (2) information was compiled before September 21, 2012, in this priority area; and (3) we received six to nine sets of comments from experts between January 11, 2012, and October 19, 2012. (Twenty topics in this priority area were being tracked in the system as of October 26, 2012.) We present three summaries of topics (indicated below with an asterisk) that emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

### Priority Area 11: Peptic Ulcer Disease and Dyspepsia

Topic	High-Impact Potential
1. *Helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis	Moderately high
2. *PerOral Endoscopic Myotomy for treatment of esophageal achalasia	Moderately high
3. Rifaximin for treatment of nonconstipating irritable bowel syndrome	No high-impact potential at this time
4. *Teduglutide (Gattex) for treatment of short bowel syndrome	Moderately high
5. Vedolizumab for treatment of moderate to severe ulcerative colitis	No high-impact potential at this time

## Discussion

Compared with other priority areas, relatively few leads and topics have been identified in this priority area that meet inclusion criteria for the horizon scanning system. Most research activity in this priority area focuses on drugs and biologics for irritable bowel syndrome and inflammatory bowel disease (e.g., Crohn’s disease, ulcerative colitis [UC]). Of the five topics on which experts provided comments, three emerged as having some potential for high impact. Helminthic therapy is notable for its novelty and ability to potentially address a serious unmet need for nonsurgical, effective treatment for severe UC. Experts deemed teduglutide as notable for its potential to restore bowel function in patients with short bowel syndrome (SBS), potentially improving quality of life and reducing costs and complications associated with parenteral nutrition (PN). And endoscopic

myotomy was deemed notable because it is minimally invasive with potential to also minimize scarring, pain, and recovery time for patients with esophageal achalasia.

## **Helminthic Therapy (Pig Whipworm) for Treatment-Resistant Ulcerative Colitis**

- **Key Facts:** Currently, no “cure” has been established for UC, a debilitating autoimmune condition that can require surgery if it becomes severe and refractory to medical treatment. From 10% to 40% of affected patients are reported to have an inadequate response to available medical therapy. For these patients, surgical colectomy is indicated. Patients sometimes also use alternative therapies. A biologic therapy, helminthic therapy (*Trichuris Suis* Ova [TSO] Suspension, Ovamed GmbH, Barsbüttel, Germany), is being used by some clinicians and patients as a nonsurgical therapeutic alternative for treatment-refractory UC. (The therapy has also recently been identified as being explored for other autoimmune diseases such as treatment-refractory multiple sclerosis, lupus, and rheumatoid arthritis.) The therapy involves self-infecting with laboratory-grown parasitic worms (helminths), which are purported to counteract severe disease symptoms. The rationale for this treatment stems from observing that inflammatory bowel diseases are rare in developing countries where helminths are common and that people have altered immunologic responses in the gastrointestinal tract when infected with helminths. Reports from observational studies suggested that helminths might prevent or improve UC by inducing production of regulatory T cells and modulatory cytokines, which then reduce inflammation. The therapy has become available by mail order in the United States with a physician prescription. The U.S. Food and Drug Administration (FDA) in 2009 issued guidance to its field district officers regarding helminthic therapy indicating that districts “may detain without physical examination all imported *Trichuris suis* ova (TSO); Pig Whipworm Eggs or Pig Whipworm Egg suspensions because these articles appear to be biological products for which a biologics license is not in effect under section 351 of the Public Health Service Act ...” It does not appear that the manufacturer intends to seek FDA regulatory approval for the therapy. Patients with severe UC report paying \$300–\$4,700 for a 10-week dose of pig whipworms ordered from outside the United States.
- **Key Expert Comments:** Overall, experts commenting on this topic were cautiously optimistic about the therapy’s potential, based on preliminary data, although they noted the potential for controversy owing to TSO’s origin. TSO has the potential to disrupt current care and cost models for UC treatment and would have a greater impact if controlled trials demonstrated the treatment to be effective in patients with UC refractory to secondary treatment agents such as corticosteroids and biologic therapies.
- **Potential for High Impact:** Moderately high

## **PerOral Endoscopic Myotomy for Treatment of Esophageal Achalasia**

- **Key Facts:** Esophageal achalasia is characterized by prolonged occlusion of the lower esophageal sphincter (LES) and reduced peristaltic activity, making it difficult to swallow food and possibly leading to complications such as regurgitation, coughing, choking, aspiration pneumonia, esophagitis, ulceration, and weight loss. Open surgical treatment for achalasia generally requires at least five abdominal incisions to access the blocked esophageal pathway, which can result in significant recovery time, complications, and pain. PerOral Endoscopic Myotomy (POEM) is a novel endoscopic procedure developed by a

Japanese surgeon, Haru (Haruhiro) Inoue, M.D. It uses a natural orifice as an entry point for surgical instruments, with the intention of reducing the total number of incisions needed and, thus, the overall invasiveness. POEM is performed with the patient under general anesthesia. After tunneling an endoscope down the esophagus toward the esophageal gastric junction, a surgeon performs the myotomy by cutting only the inner, circular LES muscles through a submucosal tunnel created in the proximal esophageal mucosa. POEM differs from laparoscopic surgery, which involves complete division of both circular and longitudinal muscle layers of the LES. Cutting the dysfunctional muscle fibers that prevent the valve at the base of the esophagus from opening allows food to enter the stomach more easily. In this report, three case series of patients with achalasia treated with POEM were highlighted (n=56, n=205, and n=31). Treatment success occurred in greater than 90% of cases in each study. POEM did not lead to any reported serious complications. In a fourth, nonrandomized historical control study, POEM investigators reported that the procedure resulted in shorter operative times and less blood loss than laparoscopic Heller myotomy (LHM), although myotomy lengths, complication rates, length of stay, and narcotic use were similar between treatments. Some speculate that because it involves cutting only one muscle layer at the LES, POEM might not be as effective as laparoscopic surgery in the long term, and revisional surgery might be difficult. Five U.S. academic medical centers initiated clinical protocols for POEM and perform the procedure under an Institutional Review Board-approved research protocol. At the 2012 meeting of the Society of American Gastrointestinal and Endoscopic Surgeons, leading researchers presented a didactic training course with reports on outcomes of cases performed to date. The U.S. centers have performed more than 80 the estimated 700 POEM cases reported worldwide since 2008. Fifteen active POEMs trials were registered at the National Clinical Trials database as of November 2012, with seven U.S. centers currently participating in or sponsoring trials. Search results did not yield cost data on POEM; theoretically it could reduce the cost of care by reducing hospital stay and complications. Although POEM is in very early diffusion, at least one major third-party payer covers the treatment for achalasia if the condition results in malnutrition.

- **Key Expert Comments:** Overall, experts commenting on this topic stated that POEM could provide a permanent, minimally invasive treatment option for achalasia with fewer incisions than laparoscopic surgery, leading to shorter recovery times and less pain. In the absence of randomized controlled trials or long-term trials, some experts were uncertain of POEM's impact potential. Overall, the experts assumed that if POEM remains an inpatient procedure with general anesthesia, the impact beyond scarring and pain reduction could be minimal. If POEM can be adapted to an outpatient procedure, costs could be lowered, and more patients might become eligible for the surgery or elect to undergo surgical treatment of their achalasia rather than receiving other nonsurgical treatment. POEM could also renew clinical interest in natural orifice transluminal endoscopic surgery (known as NOTES) if it can demonstrate better outcomes than laparoscopic surgery.
- **Potential for High Impact:** Moderately high

## **Teduglutide (Gattex) for Treatment of Short Bowel Syndrome**

- **Key Facts:** SBS encompasses a group of health problems, related to malnutrition, that occur in individuals who have lost at least half of their small intestines. Frequently, SBS arises from the surgical removal of diseased bowel portions. A shortened bowel results in diarrhea, fatigue, abdominal pain, bloating, heartburn, and nutrient deficiencies. Treatment for severe



SBS may involve oral rehydration solutions, intravenous nutrition delivery, and liquid food (PN) delivered through feeding tubes. An estimated 10,000–20,000 children and adults in the United States receive at-home intravenous nutritional support for SBS, based on data from the early 1990s, at a cost of more than \$100,000 per patient per year. One study estimated that, in pediatric patients, the mean total cost of care per child with SBS over a 5-year period in the United States was \$1.6 million. The estimated mortality rate in infants with SBS is 30%. Long-term PN can lead to serious side effects such as liver damage, the risk of which increases the longer a patient is PN-dependent. No effective treatments are available to improve long-term nutritional absorption other than intestinal transplantation. Teduglutide (Gattex<sup>®</sup>, NPS Pharmaceuticals, Inc., Bedminster, NJ) is a subcutaneously administered glucagon-like peptide 2 analog purported to induce repair and regeneration of the cells lining the intestine as well as increase nutrient absorption. Phase III trials reported that patients with SBS treated with teduglutide can significantly reduce the amount of PN required. Additionally, a long-term extension trial demonstrated that some patients treated with teduglutide were able to completely stop PN. Because it is a synthetic intestinal growth factor, there has been some concern of malignancy, and malignancies have been observed in trial participants, although FDA has not requested any protocol changes to date. In 2000, teduglutide received orphan drug designation for treating SBS. In August 2011, NPS began submitting data for a new drug application to FDA for the same indication and completed the submission in December of that year. The FDA Gastrointestinal Drugs Advisory Committee voted unanimously to recommend approval of teduglutide for adults with SBS. The decision date set by FDA was December 30, 2012.

- **Key Expert Comments:** Experts commenting on this drug believe that these reductions in PN could potentially improve patient health outcomes and quality of life as well as lower costs. If teduglutide proves to be generally tolerable in patients with SBS, reductions in PN could be sufficient motivation for patients to administer the drug's daily injections, because treatment options for SBS are limited. Additional scrutiny of teduglutide's safety and its impact on cost of care is likely going forward.
- **Potential for High Impact:** Moderately high

## **Peptic Ulcer Disease and Dyspepsia Interventions**

## Helminthic Therapy (Pig Whipworm) for Treatment-Resistant Ulcerative Colitis

No cure has yet been found for ulcerative colitis (UC). Pharmacologic therapies generally address UC symptoms' underlying inflammation; they are costly.<sup>1</sup> From 10% to 40% of patients with UC fail to respond satisfactorily to available medical therapy. For these patients, surgical colectomy is indicated.<sup>1</sup> Helminthic therapy is intended to provide a nonsurgical therapeutic alternative for patients with treatment-refractory disease.

Helminthic therapy involves self-infection with parasitic worms (i.e., helminths), which is believed to counteract severe disease symptoms. The rationale for this treatment stems from the observation that inflammatory bowel diseases are rare in developing countries where helminths are common and that people with helminths have an altered immunologic response to antigens.<sup>2</sup> Preclinical studies suggest that helminths prevent or improve UC by inducing production of regulatory T cells and modulatory cytokines, which then reduce inflammation.<sup>3</sup>

*Trichuris Suis* Ova (TSO) Suspension (Ovamed GmbH, Barsbüttel, Germany) contains microscopic porcine whipworm ova that have been grown in a laboratory. According to the manufacturer, the suspension contains 500 ova per dose; it is packaged in a vial. To administer the therapy, the patient mixes the ova with juice or an electrolyte drink and swallows the solution. The company recommends a starting dose of 500 ova, taken orally once every 1–3 weeks, with titration to a 1,000 ova per dose if no response is seen after 8 weeks (4 treatments). The company notes that initial response may require several weeks and, because helminths are short-lived in humans, will require repeated dosing to maintain response.<sup>3</sup>

The TSO product is currently available and is shipped directly from the manufacturer to the patient. The company requires a letter from a physician and a statutory declaration from the importer stating that the worms are for personal use and constitute 3 months or fewer of treatment.<sup>4</sup> The company then directs patients to a Web site to order the product, at a cost of roughly \$485 for three vials, plus shipping.<sup>4</sup> Patients with severe UC report paying \$300–\$4,700 for a 10-week dosage of pig whipworms ordered from outside the United States.<sup>5-7</sup>

The U.S. Food and Drug Administration (FDA) has issued the following guidance to its field district officers regarding helminthic therapy:

Districts may detain without physical examination all imported *Trichuris suis* ova (TSO); Pig Whipworm Eggs or Pig Whipworm Egg suspensions because these articles appear to be biological products for which a biologics license is not in effect under section 351 of the Public Health Service Act and thus appear to be new drugs under the meaning of section 201(p) of the FD&C [Federal Food, Drug, and Cosmetic] Act without an effective new drug application approval, as required by section 505 of the FD&C Act. These unlicensed biological products appear to be offered for import for the treatment of Crohn's Disease and other inflammatory bowel diseases.<sup>8</sup>

The manufacturer does not appear to intend to seek FDA regulatory approval for the therapy.

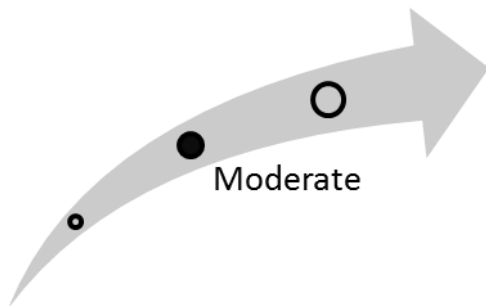
In a small study of patients (n=4) with UC who underwent a single dose (2,500 ova) of helminthic therapy, patients experienced an average reduction of the Clinical Colitis Activity Index to 57% of baseline, and no adverse events were seen during the 28-week followup period, the authors reported.<sup>9</sup> In a larger study of 54 patients with UC, patients improved in their Crohn's Disease Activity Index scores, and again, no side effects were seen.<sup>2</sup>

## Clinical Pathway at Point of This Intervention

For patients with mild to moderate UC, treatment guidelines recommend the use of oral aminosalicylates, oral prednisone, topical agents (e.g., mesalamine, corticosteroids), and/or anti-inflammatory treatments (i.e., sulfasalazine, olsalazine, mesalamine). For patients with severe UC or UC that fails to respond to standard care, infliximab infusion is typically administered. Patients who experience toxicity require hospitalization and corticosteroid infusion. If the patient does not improve after 3–5 days, colectomy (i.e., surgical removal of the colon) can be necessary.<sup>10</sup>

Helminthic therapy is intended for patients with treatment-resistant UC who have not undergone colectomy. However, in some clinical trials, patients who were given TSO also received concomitant corticosteroids in low to medium doses, and the manufacturer claims that this combination therapy was safe.<sup>3</sup> Therefore, helminthic therapy has the potential to either compete with or complement the use of anti-inflammatory drugs, immunosuppressive drugs, and biological therapies that target the immune system, particularly in patients whose disease is unresponsive to treatment. Helminthic therapy may also compete with over-the-counter drugs and herbal medications, which patients often seek out if standard treatment for UC fails to reduce their symptoms.<sup>11</sup>

**Figure 1. Overall high-impact potential: helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis**



Overall, experts commenting on this intervention were cautiously optimistic about TSO's potential to address the important unmet need of treatment-refractory UC. Although some patients and clinicians may quickly adopt the procedure, TSO has the potential to be controversial, and the treatment could disrupt current care and cost models. Experts opined that more empirical data and patient education could be necessary before this intervention would become widely diffused for this indication. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention during two different review cycles.<sup>12-25</sup> Experts agreed that the lack of curative or effective noninvasive therapies for UC, a chronic illness that can lead to lifelong morbidity and reduced quality of life in many patients, represents an important unmet need. One expert representing a clinical perspective stated that if TSO continues to demonstrate efficacy in trials, the intervention could become the second-line therapy of choice for UC. The expert also stated that TSO seemed less likely to be effective in patients whose condition is refractory to immunomodulators, corticosteroids, and tumor necrosis factor inhibitors. However, if TSO shows efficacy in that difficult-to-treat patient population, it could greatly add to the intervention's ability to address a significant unmet need.

Experts were generally encouraged by the available data for TSO, but there was general agreement that more data are needed to determine the intervention's ability to improve health outcomes. One clinical expert expressed concern that if patients were on immunosuppressive therapy, TSO treatment could potentially lead to infestation, because the parasite may behave differently in patients on immunosuppressive therapy.

TSO is not expected to greatly affect health disparities; experts noted that its simple oral administration could reduce barriers to care, but lack of third-party payment was cited as potentially adding to health care disparities.

TSO is not expected to make major changes in health care infrastructure or patient management. TSO could reduce the use of other drugs, but it could also be used as an additive therapy. Frequent followup after TSO administration may be offset by fewer visits later to address disease progression. Additionally, reductions in the demands on surgical staff and facilities that perform colectomy could be observed.

Overall, the experts stated, UC is a challenging condition for both patients and clinicians. Although the general public could find the intervention unpalatable, patients with UC typically have a host of gastrointestinal disorders and would be more accepting of TSO if it is effective and continues to be highly tolerable. Additionally, clinical experts stated that patients with UC try to avoid immunosuppressive therapy and are already seeking "natural" remedies to treat the disease. Some experts suspect that TSO can be easily integrated into their desired treatment paradigms. If patients are receptive to TSO, clinicians are also expected to have a higher acceptance if the treatment continues to be well tolerated. Conversely, an expert representing a research perspective stated that a significant cohort of clinicians probably will not accept this intervention until researchers develop a significant evidence base. The expert also stated that many patients believe that all parasites are bad and would require significant education to accept this intervention. One clinical expert postulated that religious barriers to TSO acceptance (because of the porcine connection) in patients with UC could be overstated.

The experts stated that patients with UC have significant costs associated with managing their disease. TSO is expected to reduce the cost of care if it can reduce the need for long-term pharmacotherapy or surgery.

Overall, the experts stated, UC is a condition with no cure; pharmacologic and surgical treatments for UC are costly and have significant side effects. Early results of TSO are encouraging; however, larger trials will be needed to improve patient and clinician acceptance as well as define appropriate use of TSO in the clinical pathway. TSO's impact is perceived to be dependent on further demonstration of safety and efficacy and the extent to which patients with UC refractory to steroids or biologic agents can benefit.

## PerOral Endoscopic Myotomy for Treatment of Esophageal Achalasia

Current surgical treatment for esophageal achalasia generally requires at least five abdominal incisions to access the blocked esophageal pathway, which can result in significant recovery time and complications.<sup>26,27</sup> About 3,000 cases of esophageal achalasia are diagnosed annually.<sup>27</sup> Achalasia is characterized by prolonged occlusion of the lower esophageal sphincter (LES) and reduced peristaltic activity, making it difficult to swallow food. It can lead to complications such as regurgitation, coughing, choking, aspiration pneumonia, esophagitis, ulceration, and weight loss.<sup>28</sup>

POEM is a novel endoscopic procedure that uses a natural orifice as an entry point for surgical instruments, with the intention of reducing the total number of incisions needed and, thus, the overall invasiveness.<sup>27</sup> POEM is performed with the patient under general anesthesia.<sup>26</sup> A surgeon inserts an endoscope into the patient's mouth and tunnels it down the esophagus toward the esophageal gastric junction. Then the myotomy is performed by cutting only the inner, circular LES muscles<sup>29</sup> through a submucosal tunnel created in the proximal esophageal mucosa.<sup>30</sup> This differs from current surgical technique, which involves complete division of both circular and longitudinal LES muscle layers.<sup>30</sup> Cutting the dysfunctional muscle fibers that prevent the LES from opening is intended to allow food to more easily enter the stomach.<sup>27</sup> Gastrointestinal and endoscopic surgeons perform POEM. It is purported to be an extremely sophisticated and demanding technique, even for experienced endoscopists.<sup>30</sup> Treatment options for esophageal achalasia must be carefully selected based on a patient's disease severity and surgical risk status. However, a minimally invasive procedure such as POEM might offer potential benefits including greater surgical precision, a shorter recovery time, shorter hospital stay, less pain, and a lower incidence of reflux after the procedure.<sup>27</sup>

In a published case series of patients with achalasia treated with POEM (n=56), symptoms of dysphagia were significantly reduced or disappeared in all cases.<sup>31</sup> The average myotomy length was 11.2 cm (range 5–22 cm). Resting LES manometric pressure changed from 52.5 mm Hg before POEM to 19.8 mm Hg after the procedure. No specific complications related to the surgery were experienced. During the followup period, one patient required 20 mm balloon dilatation 1 month after POEM, which was successful in treating mild dysphasia. In this study, three patients had received surgical myotomy prior to POEM (2 LHM, 1 thoracoscopic myotomy). These patients gained symptomatic control following POEM. During the followup period (up to 25 months) no patient reported dysphagia recurrence, but some patients reported mild chest pain. Four patients had endoscopically visible gastroesophageal reflux disease (GERD). In three patients, GERD symptoms were controlled with proton pump inhibitors.<sup>31</sup>

In results of another retrospective study of patients with achalasia (n=205) treated with POEM, investigators reported that 98.5% of patients were successfully treated. POEM was ineffective in 3 patients due to severe submucosal fibrosis attributed to previous therapies. The mean operation time was 68.5 minutes (range 10–180 minutes) and the average length of myotomy of inner circular muscle was 9.5 cm (range 7–13 cm). No serious complications resulted from POEM.<sup>32</sup>

In a third report of patients with achalasia (n=31) treated with POEM, the success rate was 94%. Two patients had recurrent symptoms at 3 months and both responded to pneumatic dilation. Mean myotomy length was 8.6 cm (range 3–14 cm), mean procedure time was 145 minutes (43–240 minutes), and mean length of stay was 2.2 days (1–5 days). Mean postprocedure followup was 8.4 months. Significant reductions in Eckardt score (1.1–7.5,  $p<0.0001$ ) and LES pressure (19–49 mmHg,  $p<0.0001$ ) were observed. No complications requiring intensive care, hospital stays longer than 5 days, surgical or interventional radiology interventions, blood transfusions, surgical

conversion, or POEM-related readmissions occurred. Eighty-seven percent of patients treated with POEM reportedly did not require posttreatment analgesia.<sup>33</sup>

In a nonrandomized, historical control trial, investigators reported that patients with achalasia were treated with POEM (n=18) or LHM (n=55).<sup>34</sup> Operative times were shorter for POEM versus LHM (113 and 125 minutes, respectively,  $p<0.05$ ). Additionally, estimated blood loss was less in patients treated with POEM ( $\leq 10$  mL in all cases vs. 50 mL,  $p<0.001$ ). Myotomy lengths, complication rates, and length of stay were similar between groups. Pain scores were similar upon postanesthesia care and postoperatively on day 1, but were higher at 2 hours for POEM patients (3.5 vs. 2.0,  $p=0.03$ ).<sup>34</sup> Narcotic use was similar between groups, although fewer patients treated with POEM received ketorolac.<sup>34</sup>

POEM has been generally well tolerated according to reports from studies thus far.<sup>35</sup> However, the procedure carries the usual risks associated with surgery—such as those associated with general anesthesia, and infection—and risks of other natural-orifice transluminal endoscopic surgery (NOTES) procedures. Because POEM involves cutting only one layer of muscle at the LES, some speculate that it may not be as effective long term as laparoscopic surgery and that revisional surgery might be difficult, involving extensive procedures such as esophagectomy.<sup>30</sup>

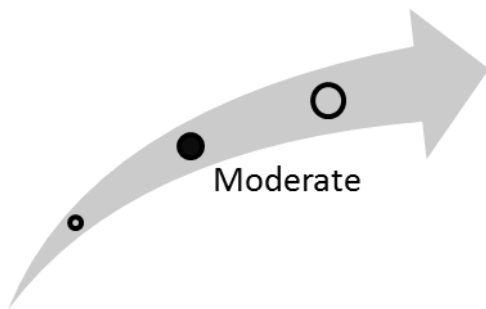
POEM uses available laparoscopic instrumentation and, as a surgical procedure, is not subject to FDA regulation. In the United States, the surgery is being performed by at least seven academic teaching hospitals through Institutional Review Board-approved clinical trial protocols. Fifteen active POEMs trials were registered in the National Clinical Trials database as of November 2012, with seven U.S. centers currently participating in or sponsoring trials.<sup>32,33,35-37</sup> These U.S. centers have performed more than 80 of the estimated 700 POEM cases reported worldwide since 2008.<sup>38</sup> At the 2012 meeting of the Society of American Gastrointestinal and Endoscopic Surgeons, leading researchers presented a didactic training course with reports on outcomes of cases performed to date.<sup>39</sup>

Search results did not identify POEM costs. However, adding endoscopy to the myotomy procedure is expected to increase costs, although a shorter hospital stay could offset those increases.<sup>40</sup> The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for POEM, and we identified no private third-party payers that publish their medical coverage policies and mention coverage of POEM.

## **Clinical Pathway at Point of This Intervention**

Esophageal achalasia is typically diagnosed by the manometric detection of swallow-related relaxation of the LES and loss of peristalsis within the tubular esophagus.<sup>30</sup> The American College of Gastroenterology recommends surgery as the primary therapy in patients with a low risk of complications from undergoing surgery. Laparoscopic myotomy with fundoplication is considered the gold standard therapy for achalasia, and it has replaced open Heller myotomy.<sup>30,41</sup> The standard surgical technique involves complete division of both circular and longitudinal muscle layers.<sup>30</sup> Other treatment options include endoscopic balloon dilation and endoscopic botulin toxin injection.<sup>26</sup> Pharmacologic options include using nitrates and calcium channel blockers.<sup>28</sup> POEM is intended to be less invasive than current laparoscopic techniques, possibly reducing complications and pain.

**Figure 2. Overall high-impact potential: PerOral Endoscopic Myotomy for treatment of esophageal achalasia**



POEM is a novel procedure that could provide a permanent, minimally invasive treatment option with shorter recovery time and less pain than current surgical options for achalasia. In the absence of results from randomized or long-term trials for POEM, some experts remain unsure how impactful POEM will be, although the growth in the number of registered clinical trials in 2012 signals marked interest in the procedure. The experts who commented generally assumed that if POEM remains an inpatient procedure with general anesthesia, the impacts beyond scarring, pain, and shortened hospital stay could be modest. If the procedure becomes an outpatient procedure, as one clinical expert from a facility with POEMs experience noted, the care setting change could represent a paradigm shift in treatment, costs savings might be achieved, and more patients could become eligible for, or elect surgical treatment. Additionally, POEM could renew interest in NOTES procedures and instrumentation if ongoing trials demonstrate better outcomes than other surgical options. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## **Results and Discussion of Comments**

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.<sup>42-48</sup> The experts stated that current treatment options for achalasia have benefits and risks associated with each respective option. All of the experts except the two representing health systems and research perspectives stated that a significant unmet exists need for a less-invasive, less-painful, less-expensive treatment option with a shorter recovery time and faster return to normal activity. One clinical expert stated that POEM could satisfy all of these unmet needs. Excluding this clinical expert, most experts who commented were less certain of POEM's efficacy because of a lack of randomized controlled trials. Two experts stated that POEM could reduce health disparities because of shorter inpatient stays, which would limit lost work days and costs. Another expert representing a health systems perspective stated that POEM could increase health disparities because the procedure would be performed only in specialty centers.

Most of the experts did not think that POEM would significantly change many aspects of health care infrastructure and patient management because no new infrastructure is needed, other than surgeon training in how to perform the procedure. Experts expected achalasia's relative rarity to minimize the impact on infrastructure and staffing if the procedure were to become standard of care. However, one clinical expert stated that POEM has a large disruptive potential based on the expert's clinical experience. The expert stated that POEM could be performed in an endoscopy suite under moderate sedation and could eventually be performed on an outpatient basis. Thus, gastroenterologists could provide "one-stop shopping for achalasia care," which differs from the current care model. Additionally, this expert stated that patients valued the lack of postoperative restrictions and lack of visible incisions. Additionally 75% of patients reported no pain after POEM, based on experience at the expert's facility.



Some of the experts stated the steep learning curve and the lack of randomized trials could be a barrier to clinician acceptance. However, the experts stated that patients are likely to accept a less-invasive procedure. One clinical expert stated that some patients will still prefer quick outpatient procedures such as balloon dilation or Botox<sup>®</sup> injections.

One clinical expert stated that in that expert's experience, clinicians are eager to learn the procedure, and no patients have rejected the opportunity to enroll in an ongoing POEM trial. The expert stated that after the procedure, patients have been highly satisfied with the results. The expert stated the facility required 20 procedures to be proficient in POEM, and the ideal practitioner would be experienced in LHM and proficient in flexible endoscopy. The experts stated that POEM is not likely to affect the cost of care much, unless the procedure can significantly shorten the length of patient stay. If POEM can eventually be performed on an outpatient basis, significant cost savings could be realized. One clinical expert stated that POEM has reinvigorated interest in NOTES procedures and instrumentation because it is the only procedure demonstrating potential to have better outcomes than laparoscopic alternatives.

## Teduglutide (Gattex) for Treatment of Short Bowel Syndrome

Short bowel syndrome (SBS) encompasses a group of health problems related to malnutrition that occurs in individuals who have lost at least half of their small intestines. The primary cause of SBS is surgical removal of more than half of the small intestine because of disease, injury, or birth defects.<sup>49</sup> About 70% of patients with Crohn's disease require at least one surgical procedure during their lifetimes to remove damaged intestine, leaving them at risk of complications such as SBS.<sup>50</sup> SBS can cause diarrhea, fatigue, abdominal pain, bloating, heartburn, and nutrient deficiencies.<sup>49</sup> An estimated 10,000–20,000 people in the United States receive at-home intravenous nutritional support for SBS based on data from the early 1990s, at a cost of more than \$100,000 per patient per year.<sup>51</sup> One study estimated that, in pediatric patients, the mean total cost of care per child with SBS over a 5-year period was \$1.6 million.<sup>52</sup> The estimated mortality rate in infants with SBS is 30%.<sup>53</sup> Long-term parenteral nutrition (PN) can lead to serious side effects such as liver damage, the risk of which increases the longer a patient is PN-dependent.<sup>54</sup> No effective long-term treatments are available to improve nutritional absorption other than intestinal transplant.

Teduglutide (Gattex<sup>®</sup>, NPS Pharmaceuticals, Inc., Bedminster, NJ) is intended to provide several critical actions throughout the gastrointestinal tract for treating SBS, including suppressing gastric motility; stimulating intestinal nutrient transport, intestinal blood flow, and crypt cell proliferation; inhibiting crypt cell apoptosis (programmed cell death); and enhancing gut barrier function.<sup>50</sup> Teduglutide is a subcutaneously administered (0.05 mg/kg of body weight/day) glucagon-like peptide 2 (GLP-2) analog, containing a single amino-acid substitution that is purported to render it resistant to dipeptidyl peptidase-4, thus significantly increasing the biologic half-life and activity of teduglutide.<sup>55,56</sup> As a GLP-2 agonist, teduglutide is purported to induce repair and regeneration of the cells lining the intestine as well as increasing the size and density of intestinal villi in the intestinal epithelial layer, resulting in better absorption of nutrients.<sup>55,56</sup>

In results of a randomized, double-blind, placebo-controlled, phase III trial, investigators reported that 63% of patients (n=43) given teduglutide (subcutaneous injections 0.05 mg/kg, daily) responded to treatment ( $\geq 20\%$  reduction from baseline in weekly PN and/or intravenous fluid volumes) versus 30% of patients (n=43) given placebo (p=0.002).<sup>57</sup> At week 24, patients who received teduglutide experienced an average 4.4 liter reduction in weekly parenteral support/PN (baseline 12.9 liters) compared with patients who received placebo, who experienced an average 2.3-liter reduction in fluids required (baseline of 13.2 liters; p $\leq 0.001$ ). After 24 weeks of treatment, 54% of patients treated with teduglutide were able to reduce the number of infusion days per week by 1 or more days, compared with 23% of patients treated with placebo (p=0.005).<sup>57</sup>

In an open-label extension trial, reductions in PN volume continued to be observed in patients treated with teduglutide and three patients were completely weaned from PN after 6.5, 8.0, and 9.0 months of teduglutide treatment, respectively.<sup>58</sup> In an interim analysis of the open-label extension trial enrolling patients with SBS who were treated with either teduglutide (n=34) or placebo for 12 months, investigators reported that 91% of patients given teduglutide were responders (achieved 20% to 100% reduction in PN and/or intravenous volume from baseline). Additionally, after 12 months of treatment with teduglutide, 53% of patients reduced their infusion days per week, and 24% of patients reduced their infusion days per week by 3 or more days. The mean reduction in the volume of PN and/or intravenous fluids was 5.2 liters per week from pretreatment baseline.<sup>59</sup> As of October 2012, the manufacturer reported, 12 patients (14%) had achieved independence from PN or intravenous support while using teduglutide.<sup>60</sup> Nine patients discontinued the trial because of adverse events. Additionally, three cases of cancer (a metastatic adenocarcinoma of probable gastrointestinal origin, nonsmall cell lung carcinoma, and squamous cell lung carcinoma) were

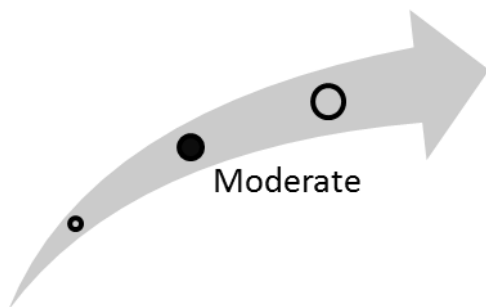
observed during the study. These malignancies were reviewed by an independent safety review board that requested no changes to the study protocol.<sup>59</sup>

In 2000, NPS received orphan drug designation for teduglutide for treating SBS.<sup>61</sup> In December 2011, NPS completed submission of a new drug application for the same indication, which FDA accepted in January 2012.<sup>62,63</sup> In October 2012, the FDA Gastrointestinal Drugs Advisory Committee voted unanimously to recommend approval of teduglutide for treating SBS in adults.<sup>60</sup> A decision was expected from FDA by December 30, 2012.<sup>60</sup> Teduglutide is not approved for any indication by FDA or the European Medicines Agency.

## Clinical Pathway at Point of This Intervention

Mild SBS can be treated by eating small and frequent meals, taking nutritional supplements, and using medication to manage diarrhea. Moderate SBS may also require using intravenous electrolyte and fluid supplements. Treatment for severe SBS may involve oral rehydration solutions, intravenous nutrition delivery, and liquid food delivered through feeding tubes. In very severe cases, intravenous nutrition can be required indefinitely.<sup>49</sup> In cases in which an obstruction in the intestine or extreme shortening of the small intestine exists, surgical options can enhance the surface area of the intestine or lengthen the time food spends in the intestines, which increases nutrient absorption.<sup>64</sup> Recombinant human somatropin (Zorbtive<sup>®</sup>) can also be used to increase absorption of nutrients; however, somatropin has not been evaluated for longer than 4 weeks in patients with SBS.<sup>65</sup> Patients with SBS who cannot be maintained on PN are potential candidates for intestine transplantation.<sup>54</sup>

**Figure 3. Overall high-impact potential: teduglutide (Gattex) for treatment of short bowel syndrome**



Teduglutide has been evaluated in only a small number of patients, yet most experts who commented were optimistic about its potential to reduce the frequency of PN administration in patients with SBS. A reduction in PN might significantly improve patient outcomes and quality of life. It might also reduce the cost of home care and complications associated with PN. SBS affects a relatively small number of patients, but those with SBS are significantly affected and have few treatment options. However, teduglutide is unlikely to obviate completely the need for PN in most SBS patients. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.<sup>66-71</sup> The experts noted that although SBS affects a small patient population, limited treatment options are available, and treatments that can reduce the need for PN are important because of its impact on quality of life and high costs. Overall, experts were optimistic regarding the ability of teduglutide to reduce the need for PN, an important outcome. Additionally, one expert

representing a clinical perspective stated that no therapies are currently available to promote the growth of villi in the intestine; thus, approval of teduglutide would mark a major advance in therapy for SBS. However, experts were divided on whether teduglutide would lead to more significant improvements in health outcomes such as weight gain, improvements in lean muscle mass, general well-being, and other quality-of-life measures. Some experts were also unsure if reductions in PN would be enough to outweigh adverse events observed in patients taking teduglutide, although one expert representing a clinical perspective stated decreasing PN has been directly correlated with improving health outcomes by reducing morbidity and mortality from central line catheter–related infections and thrombosis.

Two experts representing a clinical perspective stated that PN is difficult to administer to patients with poor access to care and that the number of medical centers performing small bowel transplants is limited. Thus, a daily self-administered injection of teduglutide, prescribed by a gastroenterologist, could help patients with poor access to care better manage their SBS, reducing health disparities.

Experts stated that using self-administered teduglutide might disrupt current models of patient management by reducing the frequency of home-care visits for PN and inpatient/outpatient admissions due to complications from PN therapy. Patients or caregivers would need to learn how to administer injections, although one clinical expert stated that many SBS patients already take injectable blood thinners. Because the population of patients is relatively small, the experts do not see a large impact to the health care system in terms of infrastructure or staffing.

In general, the experts expected teduglutide to be widely accepted by clinicians if the drug continues to show favorable efficacy and acceptable long-term tolerability, because of the limited options for SBS. The drug is also expected to be widely accepted by patients. Two experts representing a clinical perspective stated that patients with SBS are usually quite savvy regarding treatment options, frequently have a home-care team in place, and are already capable of administering subcutaneous injections. One expert representing a clinical perspective stated that reductions in PN alone could be enough to spur acceptance by patients if tolerability is acceptable. But another expert representing a clinical perspective stated that patient acceptance for teduglutide could be limited because of the need for daily injections and potential adverse events contrasted against the modest reductions in PN. The experts were generally unsure how teduglutide would affect cost of care because information about its expected cost has not yet been developed. Some experts stated the drug could reduce the cost of care if it could significantly reduce PN, although other experts stated that any changes would be minimal to the health care system because of the relatively small patient population with SBS. One clinical expert stated that controversy could arise as the potential cost-effectiveness of teduglutide and third-party coverage become known.

Although teduglutide has been evaluated in only a small patient population, most of the experts were optimistic regarding the potential for teduglutide to reduce the need for PN, which could significantly improve patient outcomes and quality of life as well as reduce the cost of care for this condition by reducing home care and complications associated with PN. Although SBS is seen in only a small patient population, those with the disease are significantly affected and have few treatment options; thus, it would likely be welcomed. Additionally, medical advances are now allowing children with conditions that put them at risk of SBS to lead longer lives, resulting in a greater need for improved long-term treatment options for SBS.

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